UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: September 22, 1999

MEMORANDUM

SUBJECT: Phostebupirim (PC Code 129086): HED's Response to Comments Submitted During Phase 3 (Public Comment Period). DP Barcode D254704-2.

FROM: Christina M. Jarvis, EPS
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INTRODUCTION:

Attached are HED's responses to comments received during the 60-day public comment period (Phase 3) for the organophosphorus acaricide phostebupirim. Comments were submitted to the Agency by Bayer Corporation (J. Thornton letter, 3/14/95), and are in response to HED's Dietary Risk Assessment Update (C. Jarvis memo, D254704, 4/9/99) and Occupational Exposure and Risk Assessment (R. Sandvig memo, D255284, 5/5/99). Input has been provided by Robert Fricke (toxicology) and Renee Sandvig (occupational exposure). HED has carefully reviewed Bayer's comments and will take them into consideration when revising the risk assessment.

Occupational Exposure

1.) Registrant's Comment:

The registrant agrees with the Agency that treatment of 50 to 100 acres/day represents typical and maximum use scenarios for an individual mixing /loading and applying Aztec. In addition, the registrant believes that the typical mixer/loader applicator exposure estimates calculated by the Agency are correct.

HED's Response:

The 1995 Phostebupirim RED estimated typical and maximum use scenarios for mixing/loading/applying Aztec to be 50 and 100 acres/day, respectively. Since then, the Agency has obtained new usage data from the Corn Insecticide Cluster Risk Assessment for Occupational Exposure (BEAD supplied data). This assessment stated that a tractor drawn broadcast spreader can apply granulars at a maximum rate of 213 acres per day (20 row planter) and a typical rate of 69 acres per day (8 row planter). These values are used by the Agency in the 1999 Phostebupirim Occupational Exposure Assessment.

2.) Registrant's Comment:

The registrant wants to make the Agency aware that the application window for Aztec (which coincides with the corn planting season) is 7-14 days in length with most applications being made in 10 days or less. As such, the potential for chronic exposure does not exist from an occupational standpoint.

HED's Response:

HED defines the length of short-term exposure as 1 to 7 days, intermediate-term exposure as 7 to 90 days, and long-term or chronic exposure as greater than 180 days per year. HED believes that exposure to handlers from phostebupirim is short- and intermediate-term. The registrant's comment that the application window for the Aztec formulation of phostebupirim is 7 to 14 days confirms HED's conclusion. HED agrees that there is no potential for chronic exposure, since no chronic scenarios were identified for phostebupirim.

Toxicology

3.) Registrant's Comment:

Selection of a developmental toxicity study in rabbits for establishing the acute RfD. Registrant felt that the developmental effects were secondary to cholinesterase inhibition, the most sensitive indicator of toxicity.

HED's Response:

The Hazard Identification Assessment Review Committee (HIARC) met on March 25, 1999 (Report dated April 13, 1999, HED Doc No: 013317) to evaluate the impact that the results of acute (MRID No. 43473001) and subchronic (MRID: 43656302) neurotoxicity studies in the rat would have on risk assessment endpoints. After reviewing the data, the HIARC agreed that the acute dietary endpoint should be based on the acute neurotoxicity study, and further, because the data gap for the two neurotoxicity studies was fulfilled, the 3X FQPA safety factor should be removed. The Committee felt that the acute (single dose) study was a more realistic exposure scenario than the previous developmental study in the rabbit study.

4.) Registrant's Comment:

The Registrant disagrees with the selection of a developmental toxicity study for evaluation of dermal exposure.

HED's Response: On March 16, 1995, the Less Than Lifetime committee revisited the Registrant's request to use the subacute (21-day) dermal toxicity study in rabbits instead of the developmental toxicity study to determine the endpoint for short-term dermal route of exposure. The committee reaffirmed the use of the developmental toxicity study NOEL for performance of the short-term occupational risk assessment. Further, as part of the Comprehensive Review of Organophosphates meeting held on May 12, 13, and 14, 1998, the HIARC reaffirmed the use of the developmental toxicity study in the rabbit for use in short-term dermal risk assessment. These decisions were based upon the following: 1) The NOELs from the dermal toxicity study (0.3 mg/kg/day) and the developmental toxicity study (0.1 mg/kg/day) were similar. 2) The effect observed in the developmental toxicity study was increased resorptions and fetal death, an endpoint considered to have potentially serious counterpart in humans. 3) The results of the dermal toxicity study indicate a steep dose-response curve in that the NOEL was 0.3 mg/kg/day while the LOEL was 1 mg/kg/day as indicated by convulsions in treated rabbits. As a result, even a small error may result in unacceptable risk. 4) The degree of difference noted in the NOELs from the two studies may reflect strain differences in rabbits and therefore can not be dismissed as an artifact of study design. 5) The use of rabbits to evaluate the dermal toxicity of sulfur-containing organophosphates is inappropriate. The rat is the preferred animal model.

A dermal absorption factor is required since oral values were selected for Short-, Intermediate-, and Long-term dermal risk assessments. A dermal absorption value of 100% was established by the HIARC (memorandum dated February 24, 1999, HED Doc No. 013270) based on comparison of the 21-day dermal toxicity study and the oral developmental toxicity study (both in rabbits) which indicate high toxicity by both routes at very low dose levels (1 mg/kg/day or less).

5.) Registrant's Comment:

The Registrant has two primary concerns with the inhalation exposure. 1) The NOEL of this study is very conservative since it was conducted with a highly respirable liquid aerosol of technical

phostebupirim rather than the relatively non-respirable dusts associated with the granular formulation; and 2) proposes an extrapolation of inhalation route of exposure to an equivalent oral dose for establishing inhalation exposure risk.

HED's Response:

The study selected for evaluating inhalation risk assessment is the 28-day nose-only inhalation study in rats (MRID 42005450) with technical phostebupirim. The use of the technical ingredient, rather than formulated product, is appropriate since the toxicological concerns are with the active ingredient rather than the formulated product. Differences in toxicity between technical ingredient and formulated products are addressed in the acute toxicity guidelines. Since this inhalation study was found to be acceptable, route-to-route extrapolation is not warranted.